

EXHIBIT 3 HUH
DATE 1-30-09
281

The CONTRACEPTION *Report*

July 1999
Volume 10, No. 3

What's Inside...

Using Oral Contraceptives
to Treat Medical Conditions:

Who can benefit? p. 4

Hormonal Contraception
and Sexually Transmitted
Disease:

*What does the evidence
tell us? p. 11*



Sponsored by:
Dannemiller Memorial Educational Foundation

July 1999

Executive Editor

David A. Grimes, MD

Vice President of Biomedical Affairs
Family Health International
Research Triangle Park, North Carolina
Clinical Professor, Department of Obstetrics
and Gynecology
University of North Carolina School of
Medicine — Chapel Hill, North Carolina

Associate Editors

Ernie J. Chaney, MD

Professor Emeritus, Department of
Family and Community Medicine
The University of Kansas School of
Medicine, Wichita — Wichita, Kansas

Elizabeth B. Connell, MD

Professor Emeritus, Department of
Gynecology and Obstetrics
Emory University School of Medicine —
Atlanta, Georgia

Mitchell D. Creinin, MD

Associate Professor, Department of Obstetrics,
Gynecology and Reproductive Sciences
Magee-Womens Hospital
University of Pittsburgh School of Medicine
— Pittsburgh, Pennsylvania

S. Jean Emans, MD

Chief, Division of Adolescent/Young
Adult Medicine
Children's Hospital
Associate Professor of Pediatrics
Harvard Medical School —
Boston, Massachusetts

Joseph W. Goldzieher, MD

Distinguished Professor, Department
of Obstetrics and Gynecology
Texas Tech University Health Sciences Center
— Amarillo, Texas

Paula J. A. Hillard, MD

Professor, Departments of Obstetrics &
Gynecology and Pediatrics
University of Cincinnati College of Medicine
— Cincinnati, Ohio

Luigi Mastroianni, Jr., MD

William Goodell Professor of Obstetrics
and Gynecology
University of Pennsylvania Medical
Center — Philadelphia, Pennsylvania

Managing Editor/Senior Writer:

Melinda Wallach, RN

Staff Writer: Carl Peterson, III

Editorial Assistant: Joe Simon

Creative Director: Emily Stetser

Art Director: Kathleen Mercandetti

Administrative Assistant: Diane Haweeny

Statement of Need: Continuing research into present and future methods of birth control makes it important for clinicians to stay informed about the most up-to-date findings concerning all forms of contraception. Clinicians involved in reproductive health care need to understand issues related to the use of oral contraceptives to treat medical conditions. In addition, clinicians need to be familiar with effective counseling strategies when prescribing OCs for noncontraceptive uses. They also need to be aware of the latest data regarding hormonal contraception and the risk of sexually transmitted diseases and human immunodeficiency virus.

Goal: The broad mission of the Editorial Board for *The Contraception Report* is to develop patient education and professional communication materials that address the benefits and risks of contraceptives, as well as other reproductive health-related issues, in a scientifically balanced manner.

CME continued on page 10

The Dannemiller Memorial Educational Foundation requires that the faculty participating in a continuing medical education activity disclose to participants any significant financial interest or other relationship (1) with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in an educational presentation, and (2) with any commercial supporters of the activity.

David A. Grimes, MD, has performed research supported by Berlex, Ortho, and Wyeth-Ayerst. He has been a consultant for ALZA, GynoPharma, Mead Johnson, Ortho, Schmid, and Searle. He has served on the speakers' bureaus of Berlex, GynoPharma, Ortho, Parke-Davis, and Wyeth-Ayerst.

Ernie J. Chaney, MD, is not engaged at this time in research activities supported by major pharmaceutical companies. He is a consultant and member of an advisory board for 3M and Schering Plough.

Elizabeth B. Connell, MD, has been a consultant to Imagyn, Organon, Combe, Gynecare, and UroMed. She has served on the speakers' bureaus of Wyeth-Ayerst, Berlex, Ortho, GynoPharma, Parke-Davis, Syntex, and MEDED.

Mitchell D. Creinin, MD, has performed research and has been a consultant for Wyeth-Ayerst and Ortho. He serves or has served on the speakers' bureaus of Ortho, Wyeth-Ayerst, Organon and Upjohn.

S. Jean Emans, MD, serves on the speakers' bureaus of Wyeth-Ayerst and Syntex, and her Division has received educational grants from Wyeth-Ayerst, Ortho, Pfizer, and Upjohn.

Joseph W. Goldzieher, MD, serves on speakers' bureaus for Berlex and Wyeth-Ayerst and serves as a consultant to *Monthly Prescribing Reference*.

Paula J.A. Hillard, MD, is on an advisory board for Wyeth-Ayerst and serves on the speakers' bureaus of Wyeth-Ayerst, Berlex, GynoPharma and Centeon. She has received research support from Wyeth-Ayerst and Proctor & Gamble.

Luigi Mastroianni, Jr., MD, serves on the speaker's bureau of Zeneca Pharmaceuticals. He or his division at the University of Pennsylvania has received research grants from Wyeth-Ayerst, Ortho, Zeneca, and Serono Laboratories.

Produced in cooperation with:

- Association of Reproductive Health Professionals
- Planned Parenthood® Federation of America, Inc.
- The National Association of Nurse Practitioners in Reproductive Health

The Contraception Report ©1999

Emron, 100 Campus Road, Totowa, NJ 07512 Fax 973-720-6080

Emron is a company of IMS HEALTH

This program is provided to the professional medical community through an unrestricted educational grant from Wyeth-Ayerst Laboratories.

Using Oral Contraceptives to Treat Medical Conditions

SUMMARY

Clinicians frequently prescribe oral contraceptives (OCs) for noncontraceptive medical purposes. The use of OCs for "off-label" indications is often related to the well-documented health benefits that the pill provides. OCs can treat dysmenorrhea, abnormal uterine bleeding, bleeding disorders, polycystic ovary syndrome, acne, and hirsutism. Clinicians sometimes also use OCs to prevent functional ovarian cysts, replace estrogen in amenorrheic patients, and alleviate conditions affected by the menstrual cycle, including mood swings, migraines, and seizures. Substantial evidence supports many of these uses. However, in some cases, more research is necessary to demonstrate efficacy. Use of OCs for noncontraceptive purposes also raises special counseling issues for clinicians.

Researchers have studied combined oral contraceptives extensively in the 4 decades since their introduction. This research has documented a number of noncontraceptive benefits, many of which are related to OC inhibition of ovulation and ovarian cyclicity.¹ Consequently, clinicians often prescribe OCs for purposes other than or in addition to pregnancy prevention.

The practice of prescribing a drug for indications other than those approved by the Food and Drug Administration (FDA) is both legal and common. Indeed, practitioners often prescribe medications for unlabeled uses without being aware that the indication is not approved. Acknowledging that some clinicians may be reluctant to prescribe "off-label," the FDA has clearly stated that they may prescribe drugs for unapproved uses (see box).

The American Medical Association (AMA) echoes the FDA's position on unlabeled use of medications. According to the AMA, the "prescription of a drug for an unlabeled indication is entirely proper if based on rational scientific theory, reliable medical opinion, or controlled clinical studies. The FDA has made eminently clear that it neither has nor wants the authority to compel prescribers to adhere to officially labeled uses. ... Drug labeling per se does not set the standard for what is good medical practice."² Ironically, many health insurers will cover OCs as a benefit for off-label uses such as dysmenorrhea, irregular cycles, or endometriosis, but not the labeled use of contraception.

Dysmenorrhea

One of the most common off-label uses of oral contraceptives is for relief of menstrual disorders. OC users have fewer instances of menorrhagia (excessive uterine bleeding), irregular menstruation, and intermenstrual

bleeding than women experiencing spontaneous menstrual cycles.³ OC use also improves primary dysmenorrhea in most women and premenstrual tension in some.

The usefulness of OCs in treating dysmenorrhea may be particularly beneficial for adolescents. Dysmenorrhea is a common complaint among teenagers; as many as 60% of adolescents report the condition, 14% of whom have missed school as a result.⁴

Teens have become increasingly aware of the benefits of OCs for dysmenorrhea. According to Paula J.A. Hillard, MD, Associate Editor of *The Contraception Report*, "In my experience, adolescents, in particular, are largely aware of the benefit of decreased dysmenorrhea. Often, they know someone who is on the pill to treat dysmenorrhea. It's probably the most common off-label indication of OCs."

Dr. Hillard adds that OCs should not be considered first-line therapy for dysmenorrhea for nonsexually active teens: "I tell patients that primary treatment for significant dysmenorrhea is nonsteroidal anti-inflammatories — those available over the counter and

Prescribing Drugs for Unlabeled Uses

"The [Food, Drug and Cosmetic] Act does not...limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for...uses that are not included in approved labeling. Such... 'unlabeled' uses may be appropriate...and may, in fact, reflect approaches ...that have been extensively reported in the medical literature."

—FDA Drug Bulletin
April 1982

by prescription. But, if that treatment is insufficient and girls are still missing school, then I think it's reasonable to consider the next step. For me, the next step is OCs, unless there are any contraindications."

The alleviation of dysmenorrhea among OC users may also have benefits in terms of compliance. OC users who are told about the beneficial effect on dysmenorrhea may be more likely to take their pills regularly, according to S. Jean Emans, MD, Associate Editor of *The Contraception Report*. "For adolescents who have dysmenorrhea, are sexually active, and are going on oral contraceptives, if the clinician points out that a real advantage of being on the oral contraceptive is relief of dysmenorrhea, research⁵ has shown they're much more likely to adhere to the program and will be contraceptive continuers," she explains.

Excessive or Unpatterned Uterine Bleeding

Abnormal uterine bleeding, commonly referred to as dysfunctional uterine bleeding (DUB), requires an evaluation to exclude a specific cause. The condition is defined as excessive, prolonged, unpatterned uterine bleeding in the absence of an identifiable pathologic condition.⁶ Menorrhagia is quite common, affecting about 20% of reproductive-age women.⁷ The problem is particularly prevalent among adolescents, in whom abnormal bleeding is often related to anovulatory cycles resulting from an immature hypothalamic-pituitary-ovarian axis.

OCs are used to treat heavy and intermenstrual bleeding, restore synchrony to the endometrium, and prevent long-term consequences of anovulation.⁶ Inhibiting the synthesis of estrogen receptors with synthetic progestin can reduce endometrial activity and regulate menstrual blood loss.¹ According to a recent review, however, "progestin alone...may not halt [bleeding] if the condition has been prolonged; thus, the combined estrogen-progestin oral contraceptives are more effective at stopping [bleed-

ing] that is in progress. If the patient is sexually active, the oral contraceptive is the treatment of choice."⁶

A recent Cochrane Collaboration systematic review also described the benefits of OCs for heavy menstrual bleeding: "A range of medical therapies is prescribed in order to reduce excessive menstrual blood loss, including prostaglandin synthetase inhibitors, antifibrinolytics, the oral contraceptive pill [OCP] and other hormones. Objective data have shown that, at least in the short term, considerable reduction in the volume of menses is achievable. ... When taken in a cyclical fashion, [the OC pill] induces

The recommended OC treatment regimen depends upon bleeding severity. For acute bleeding episodes, especially with anemia, researchers recommend a high-dose estrogen-progestin approach.⁹ Up to 3 or 4 OC tablets a day can be used. Once the bleeding stops, high-dose therapy is stopped, or tapered and stopped, to allow withdrawal bleeding; a lower dose is then continued for a total of at least 3 months. After the acute bleeding episode is controlled, the patient can use standard-dose OC regimens. For less acute episodes without anemia, regimens of 1 or 2 OCs a day may be successful.

***OC users who are told about
the beneficial effect on dysmenorrhea may be more likely
to take their pills regularly.***

regular shedding of a thinner endometrium and inhibits ovulation. With this method, good cycle control can be achieved and, together with the provision of contraception, this makes OCP a most acceptable longer term therapy for some women with menorrhagia."⁸

Citing insufficient data from randomized, controlled trials, the Cochrane reviewers were unable to quantify the effectiveness of oral contraceptives as treatment for irregular, heavy, or intermenstrual bleeding. Others have reported that OCs may reduce menstrual flow by up to 53%.⁶ According to Dr. Hillard, "For irregular bleeding and menorrhagia, OCs are very, very helpful. Studies show that all of the pills — including the low-dose 20 mcg ethinyl estradiol (EE) pills — decrease the number of days of flow and amount of flow. One has to consider the etiology of the irregular bleeding; but, once the etiology is sorted out, treatment with OCs is a mainstay among clinicians for women of all ages."

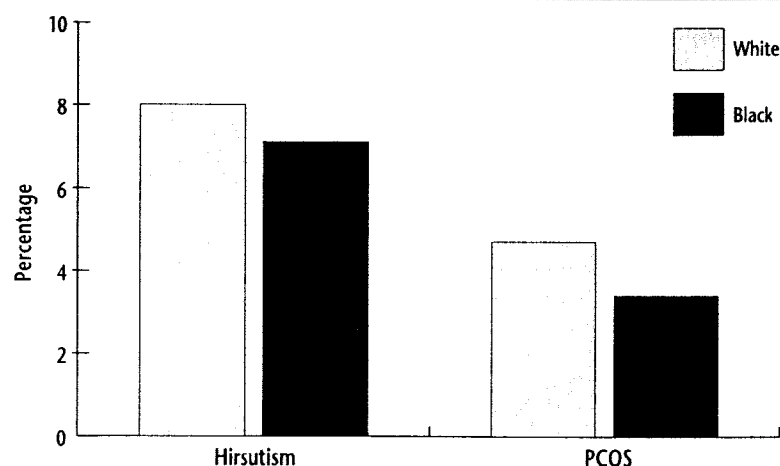
Bleeding Disorders

A small percentage of women, especially adolescents, with heavy menstrual bleeding may have bleeding disorders. According to Dr. Hillard, "Beyond abnormal menstrual periods, true bleeding disorders may occur. A very small percentage, probably less than 1% of all women, has some sort of bleeding disorder. It's a small number, but still needs to be ruled out, particularly in adolescents. Does this person have leukemia or idiopathic thrombocytopenia or von Willebrand disease?"

Oral contraceptives may be beneficial in treating bleeding disorders. According to Dr. Hillard, "OCs can be of marked benefit by actually causing a slight increase in clotting factors."

A recent review also noted the benefits of OCs for bleeding disorders, particularly von Willebrand's disease: "Von Willebrand's disease is a heterogeneous group of bleeding disorders that have in common quantitative and qualitative abnormalities of a large multimeric glycoprotein, von Willebrand's factor. ... Eighty percent

Figure 1
Prevalence of Hirsutism and Polycystic Ovary Syndrome (PCOS)
in US Women, by Race



Source: Knochenhauer ES, et al, 1998 (see reference 11).

of patients with von Willebrand's disease have type 1, in which von Willebrand's factor is present in reduced amounts but the factor that is available functions normally. ... The use of combination oral contraceptives and pregnancy both are associated with an increase in von Willebrand's factor."⁹

Polycystic Ovary Syndrome

OCs have been used to treat conditions related to excess androgens, such as polycystic ovary syndrome (PCOS). The characteristics of PCOS include a history of chronic anovulatory bleeding combined with laboratory evidence of androgen excess, such as elevated serum androgen concentrations and hyperinsulinemia. PCOS is associated with clinical characteristics of acne, hirsutism, infertility, insulin resistance, and often obesity. Because women with PCOS often have chronic estrogen exposure unopposed by progesterone, they may be at increased risk for endometrial cancer, as well.¹⁰ They also are at increased risk for the development of diabetes mellitus.

PCOS is one of the most common reproductive endocrinological disorders in women.¹⁰ A recent study¹¹ of 369 reproductive-age women reported

a PCOS prevalence of 4% and a hirsutism prevalence of nearly 8% (Figure 1). PCOS was defined as oligoovulation, clinical hyperandrogenism and/or hyperandrogenemia, and exclusion of other related disorders, such as hyperprolactinemia, thyroid abnormalities, and nonclassic adrenal hyperplasia. Hirsutism was defined by a Ferriman-Gallwey body hair quantification score of 6 or more. The study reported a slightly higher percentage of PCOS and hirsutism among white women than among black women; however, the difference was not statistically significant.¹¹

The primary goal of PCOS treatment is to alleviate symptoms. It has been speculated that the risk of sequelae also may be reduced by treatment. The most frequently used treatment approaches are ovulation induction for infertility, OCs or a progestin for menstrual irregularity, and OCs and/or spironolactone for hirsutism.¹⁰ Oral contraceptives also

can be effective in treating PCOS-induced acne.¹² Insulin sensitizing agents (eg, metformin) also have been studied to reduce androgens, induce ovulation, and as an adjunct to those with type 2 diabetes mellitus.

Acne and Hirsutism

Oral contraceptives can treat acne and hirsutism in women with and without PCOS. Combination OCs suppress ovarian, adrenal, and peripheral androgen metabolism, resulting in a net reduction in free testosterone. In addition, OCs inhibit 5 α -reductase in the skin, resulting in lower levels of the active androgen dihydrotestosterone.

The American College of Obstetricians and Gynecologists summarizes the benefits of OCs for hirsutism: "The mainstay of medical therapy [for hirsutism] is low-dose combination oral contraceptives, which effectively suppress ovarian function and reduce ovarian androgen secretion. Moreover, the estrogen in oral contraceptives stimulates hepatic synthesis of [sex hormone-binding globulin] and results in greater binding of testosterone, thus limiting its bioavailability."¹³

Numerous studies have reported acne improvement with various OC formulations. One OC has been approved by the FDA specifically for the treatment of acne in women over 15 years of age who desire contraception and are unresponsive to topical anti-acne medications. Two randomized, placebo-controlled trials found significant improvement in preexisting acne among users of this triphasic OC, which contains 35 mcg EE and norgestimate.^{14,15} The trials did not compare this pill to any other OCs.

According to Dr. Hillard, recent consumer-oriented advertising has raised awareness of OCs as acne treatment. "I think it has brought

**Oral contraceptives can treat acne and hirsutism
in women with and without PCOS.**

more patients to the clinician," she says. "Of course, when patients come to me after seeing an advertisement, I have to take time to explain to them that all OCs are good for acne for most people."

Dr. Emans agrees, adding that awareness of acne benefits has helped to destigmatize the pill, especially among adolescents: "For families to know that oral contraceptives benefit acne has made it much more acceptable for both mothers and adolescent girls to feel that the pill has a very positive effect on their lives; they're not as scared of OCs. It has had a positive effect on people continuing the pill and coming in and asking for contraception."

"I certainly explain to them that the benefit for acne is something that applies to oral contraceptives in general. It's quite possible that one particular pill, for whatever reason, is going to result in nausea or headache or some other side effect, and you don't want them to believe that the only OC that will make their acne better is a particular one that they've seen in an ad. It's incredibly important to explain that acne is improved by almost all OCs, and to take their history (such as prior OC experience) into account when prescribing a particular pill."

"OCs are not first-line treatment for acne," adds Dr. Hillard. "Clinicians will start with topical therapies, then usually move on to oral antibiotics. But, after trying those measures, if moderate or severe acne remains, OCs are probably the next step. Clearly, OCs should be considered before or concurrently with isotretinoin, given that it's a teratogen. Someone taking this acne medication needs to be on a good method of contraception; OCs are one choice."

Endometriosis

Endometriosis, which may affect up to 15% of premenopausal women, can cause pelvic pain, dysmenorrhea, dyspareunia, and infertility.¹⁶ Endometriosis most likely results from an abnormal immunologic response to

retrograde menstruation with resultant implantation of endometrial tissue in the abdomen and pelvis. Consequently, oral contraceptives and other birth control methods that alter menstrual flow may influence the development of endometriosis.

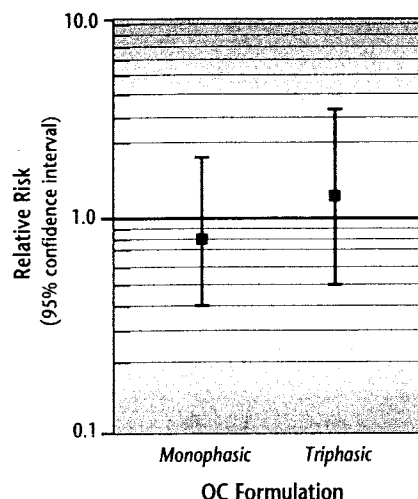
Clinicians sometimes use OCs to help reduce the pelvic pain associated with endometriosis. They also are used for long-term suppression after initial surgical and/or medical treatment. According to Dr. Hillard, "Many clinicians are using OCs as maintenance after, for example, treatment for 3 to 6 months with a gonadotropin-releasing hormone analogue." One approach, the tricyclic regimen, consists of taking 3 or 4 cycles of OCs without a break for withdrawal bleeding. This reduces menses to 3 or 4 occasions per year, thus reducing the number of opportunities for retrograde menstruation and potential additional endometrial tissue deposits and results in less frequent dysmenorrhea.

A recent Cochrane Collaboration review examined the evidence related to OC use for endometriosis pain.¹⁶ According to the reviewers, "There is a paucity of data relating to the use of oral contraceptive preparations in the treatment of symptomatic endometriosis. [However,] the data such as it is supports the common practice of the use of the oral contraceptive pill as first line therapy ... [I]t may offer an acceptable long term alternative treatment for the painful symptoms of endometriosis."¹⁶

Ovarian Cysts

Older OC formulations helped prevent the development of functional ovarian cysts.¹⁷ Newer data suggest this benefit is decreased¹⁸ or may not exist¹⁹ with lower-dose pills, however. A small (32 cases) 1992 study reported a greater protective effect against functional ovarian cysts among women using high-dose (>35 mg EE) monophasic OCs (relative risk [RR]=0.2; 95% confidence interval [CI], 0.01-1.3) than among those using low-dose monophasic pills (RR=0.5, 95% CI, 0.2-1.3).¹⁸

Figure 2
Relative Risk of a Diagnosed Ovarian Cyst Among Current Users, by OC Formulation



Source: Holt VL, et al, 1992 (see reference 19).

In a larger 1992 case-control study, current use of low-dose monophasic or triphasic OCs had no significant effect on risk of functional ovarian cyst development (Figure 2).¹⁹

"OCs are often used for prevention of functional ovarian cysts in someone who has had one or two functional cysts, be they follicular or corpus luteum cysts," explains Dr. Hillard. "Corpus luteum cysts can cause a great deal of pain, and higher-dose OCs clearly prevent cysts."¹⁷ Also, a person who has had an ovarian neoplasm probably ought to be on OCs to suppress further benign cyst development that may be confused with a recurrence of a malignancy or a benign neoplasm and to reap the benefit of a reduced risk of ovarian cancer associated with OCs."

Although some clinicians prescribe OCs to hasten the regression of existing ovarian cysts, little evidence supports this action. In a 1990 randomized, controlled trial of the effect of OC therapy on adnexal cysts in women of reproductive age, 48 patients were randomized to receive either 1 mg norethindrone/50 mcg mestranol per day or no treatment for up to 6 weeks.

At 6 weeks, the cysts had resolved in all but one patient in each group. By 9 weeks, both groups had complete resolution of their cystic adnexal masses (Figure 3). The authors concluded that "there remains little evidence that these medications are effective in hastening the disappearance of these cysts once they are formed."²⁰ Because of its small sample size, however, this trial had little power to find a benefit if it exists.

Diet- or Exercise-Induced Amenorrhea

OCs can replace estrogen in patients with hypoestrogenic amenorrhea. This condition is common among women with eating disorders or those who are involved in endurance sports, such as running. According to Dr. Emans, "We see a number of adolescents who either have an active eating disorder or had one in the past and their system isn't producing enough estrogen. We also see athletes who are underweight for height, particularly those involved in sports such as gymnastics or track — endurance sports — or girls involved in artistic endeavors such as ballet. These patients often have hypoestrogenic amenorrhea.

"Many of us prescribe estrogen, given as oral contraceptives, for these young women, although randomized studies have not been done to prove that it's effective at preventing the consequences of hypoestrogenism, such as osteoporosis. Clearly, the best therapy for these women is to get their own menses back and to gain weight, particularly if they have eating disorders. We do know that girls with severe eating disorders who become hypoestrogenic early in adolescence do not recover their bone density unless they regain their weight and menses."

Most studies of the effect of estrogen replacement on bone density have been done with postmenopausal women. The applicability of those studies to amenorrheic adolescents is not clear. A recent review concluded, "Treatment with [OCs] may have a

beneficial effect on [bone mineral density] in young women with hypothalamic amenorrhea, but this has not been established in a double-masked, randomized, controlled trial."²¹

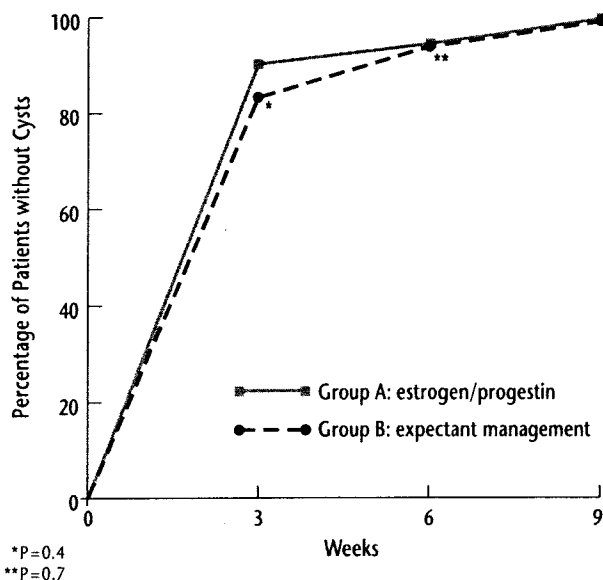
Dr. Emans adds that OCs may also benefit other amenorrheic patients. "We use oral contraceptives for estrogen replacement in other patients, and we do get good results in the young women who, for example, had bilateral oophorectomy or radiation therapy for cancer and now have ovarian failure. We often use oral contraceptives in these patients as a primary way of replacing their estrogen."

Menstrual Cycle Conditions

OCs may help a number of conditions that are linked to the menstrual cycle, including menstrual migraines, mood changes, and seizures. The sharp variations in serum estradiol and progesterone levels during the menstrual cycle (Figure 4) can trigger these conditions.²² By contrast, women using monophasic OCs have relatively constant hormonal levels throughout most of the cycle.

According to Dr. Hillard, "Some literature suggests OCs can be helpful in managing menstrual mood disorders. In this situation, one would not go with a triphasic pill; a monophasic pill would be preferable." Dr. Emans adds, "Randomized clinical trials show some benefits of OCs for premenstrual syndrome in some situations; in other cases, they don't. I merely offer it as one of multiple therapies: lifestyle changes, the use of SSRIs [selective serotonin reuptake inhibitors], or being on oral contraceptives for a few cycles to see if it helps. There are a number of patients

Figure 3
Cumulative Percentages for the Disappearance of Functional Ovarian Cysts



Source: Steinkampf MP, Hammond KR, Blackwell RE. Hormonal treatment of functional ovarian cysts: a randomized, prospective study. *Fertil Steril* 1990;54:775-777. Reproduced with permission.

in whom it does seem to have a clinical benefit."

A recent review of treatment strategies for premenstrual syndrome (PMS) reached a similar conclusion: "Hormonal contraceptive methods suppress ovulation; thus, combined oral contraceptive pills or a progestin-only contraceptive agent may provide relief of PMS. The low cost, effectiveness and reversibility of oral contraceptives favor their use. Efficacy of various contraceptive formulations for the treatment of PMS has not been compared."²³

According to Dr. Hillard, "OCs may be useful in treating other conditions that are exacerbated by menses, such as menstrual migraines. The literature is fairly sparse and some is not entirely evidence-based. Menstrual migraines can sometimes be managed by longer cycles of OCs — not 21 days of active pills, but 42 or 63 days."

Data on the relationship between OCs and migraines are mixed. OC use can induce or alleviate headache.²⁴ Women with a history of headache relief while on OCs or those with intractable menstrual migraine may be the most appropriate candidates for OC therapy.²⁴

The effects of OCs on seizures can vary, as well. According to a recent review of hormonal therapy for women with epilepsy, "Oral contraceptives and menopausal hormone replacement can exacerbate or benefit seizure disorder, depending on the particular circumstances of the treatment. ... [I]ndividual successes with continuous daily oral use of norethistrone and combination pills have been reported."²² Further studies of efficacy for lessening premenstrual seizures are needed.

According to Dr. Emans, "The pill can be used for patients with seizure disorders; some of these patients will benefit. The downside, however, is that women usually have to be on a higher dose because their metabolism of oral contraceptives is enhanced by several antiepileptic medications. In order to prevent breakthrough bleeding or ovulation, one has to tend more toward the 35 to 50 mcg pills."

Counseling Issues

Using OCs to treat medical conditions raises special counseling issues. According to Dr. Hillard, "Patients — and mothers, when we're talking about adolescents — are probably more concerned about the risks of OCs when they are taking them for noncontraceptive indications," she explains. "It should also make the clinician think a little bit differently about evaluating the risk-benefit ratio. For example, we know that OCs have a much lower risk of leading to thromboembolic phenomena than pregnancy. However, the risk-benefit assessment changes a bit because the comparison is not with pregnancy."

Dr. Emans adds that it is important for practitioners to determine and address all of a patient's concerns. "I always begin by asking patients what they've heard about the pill. If the patient is an adolescent and her mother is with her, I also ask what she's heard about it. I make sure to get their worries on the table before just assuming that I know what everyone's concerns are. What they bring up might be really different from what I'd even thought of. Their fears or concerns may be something

that I know is not related to the pill and wouldn't have addressed if I'd not asked about their worries first.

"For adolescent girls, I often ask them if any of their friends have taken the pill for irregular periods or cramps or acne. What have they heard from their friends who have taken it? We need to make sure we're getting a personalized message to these adolescents.

"I also go through the most common side effects. I present the idea of breakthrough bleeding as very common in the first 3 months, so it's more likely to be accepted. I take an actual pill package and show them the second week of the pills. I tell them it's very common for OC users to have bleeding in the second week. I tell them they should keep track of it, but they shouldn't worry about it; they should keep taking the pills.

"I also explain that some people experience some nausea the first few days of taking the pill, but many do not. I tell them that some people may have an increase or decrease in their headaches. I add that some people gain and some people lose weight, but I emphasize that the fast foods they might be eating are what contain calories — not the pill. You have to be incredibly concrete with a new pill starter, especially an adolescent.

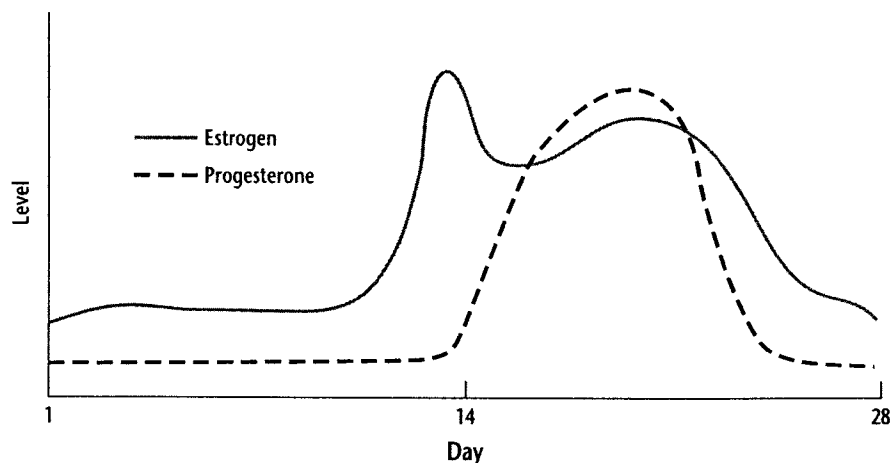
"Lastly, I ask them if they've heard anything that the pill does that's good for them. They may have heard about acne or menstrual cramps. I tell them about some of the other benefits. We also have a list of all the noncontraceptive benefits of the pill on the written instructions we give patients. It's important to let patients know that there are numerous noncontraceptive benefits and uses of oral contraceptives, regardless of the indication you're prescribing them for."

Conclusion

Oral contraceptives are often prescribed off-label for a number of medical indications. Many of these uses are related to the documented noncontraceptive benefits of OCs. For some indications, the use of OCs as

Figure 4

Relative Variation in Serum Estradiol and Progesterone Levels During the Menstrual Cycle



Source: Herzog AG. Reproductive endocrine considerations and hormonal therapy for women with epilepsy. *Epilepsia* 1991;32(suppl 6):S27-S33. Reproduced with permission.

medical treatment is supported by substantial data; other situations lack well-controlled evidence. Clinicians should take time to address patient concerns about OCs — real or perceived — prior to prescribing the pill for any purpose.

References

1. Crosignani PG, Vegetti W, Bianchedi D. Hormonal contraception and ovarian pathology. *Eur J Contracept Reprod Health Care* 1997;2:207-211.
2. American Medical Association. Prescription practices and regulatory agencies. In: *Drug Evaluations, 6th ed.* Philadelphia: W.B. Saunders; 1986:1-11.
3. Mishell DR. Noncontraceptive health benefits of oral steroidal contraceptives. *Am J Obstet Gynecol* 1982;142:809-816.
4. Klein JR, Litt IF. Epidemiology of adolescent dysmenorrhea. *Pediatrics* 1981;68:661-664.
5. Robinson JC, Plichta S, Weisman CS, et al. Dysmenorrhea and use of oral contraceptives in adolescent women attending a family planning clinic. *Am J Obstet Gynecol* 1992;166:578-583.
6. Lavin C. Dysfunctional uterine bleeding in adolescents. *Curr Opin Pediatr* 1996;8:328-332.
7. Stabinsky SA, Einstein M, Breen JL. Modern treatments of menorrhagia attributable to dysfunctional uterine bleeding. *Obstet Gynecol Survey* 1998;54:61-72.
8. Iyer V, Farquhar C, Jepson R. Oral contraceptive pills for heavy menstrual bleeding (Cochrane Review). In: *The Cochrane Library, Issue 2, 1999.* Oxford: Update Software.
9. Chuong CJ, Brenner PF. Management of abnormal uterine bleeding. *Am J Obstet Gynecol* 1996;175:787-792.
10. Guzick D. Polycystic ovary syndrome: symptomatology, pathophysiology, and epidemiology. *Am J Obstet Gynecol* 1998;179:S89-S93.
11. Knochenhauer ES, Key TJ, Kahsar-Miller M, et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998;83:3078-3082.
12. Berga SL. The obstetrician-gynecologist's role in the practical management of polycystic ovary syndrome. *Am J Obstet Gynecol* 1998;179:S109-S113.
13. American College of Obstetricians and Gynecologists. Evaluation and treatment of hirsute women. *ACOG Technical Bulletin*, 1995;203.
14. Redmond GP, Olson WH, Lippman JS, et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. *Obstet Gynecol* 1997;89:615-622.
15. Lucky AW, Henderson TA, Olson WH, et al. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997;37:746-754.
16. Moore J, Kennedy S, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis (Cochrane Review). In: *The Cochrane Library, Issue 2, 1999.* Oxford: Update Software.
17. Vessey M, Metcalfe A, Wells C, et al. Ovarian neoplasms, functional ovarian cysts, and oral contraceptives. *BMJ* 1987;294:1518-1520.
18. Lanes SF, Birmann B, Walker AM, et al. Oral contraceptive type and functional ovarian cysts. *Am J Obstet Gynecol* 1992;166:956-961.
19. Holt VL, Daling JR, McKnight B, et al. Functional ovarian cysts in relation to use of monophasic and triphasic oral contraceptives. *Obstet Gynecol* 1992;79:529-533.
20. Steinkampf MP, Hammond KR, Blackwell RE. Hormonal treatment of functional ovarian cysts: a randomized, prospective study. *Fertil Steril* 1990;54:775-777.
21. Hergenroeder AC. Bone mineralization, hypothalamic amenorrhea, and sex steroid therapy in female adolescents and young adults. *J Pediatr* 1995;126:683-689.
22. Herzog AG. Reproductive endocrine considerations and hormonal therapy for women with epilepsy. *Epilepsia* 1991;32(suppl 6):S27-S33.
23. Daugherty JE. Treatment strategies for premenstrual syndrome. *Am Fam Physician* 1998;58:183-192.
24. Silberstein SD, Merriam GR. Sex hormones and headache. *J Pain Symptom Manage* 1993;8:98-114.

CME continued from page 2

Educational Objectives: After reading this monograph, participants will be able to:

- 1) identify at least three noncontraceptive medical uses of combined OCs;
- 2) state the Food and Drug Administration's position regarding off-label use of drugs;
- 3) identify the number of new STD cases that occur annually in the US;
- 4) describe the association between hormonal contraception use and HIV susceptibility; and
- 5) explain the effects of condom use counseling on hormonal contraception users.

Educational Method: The information is presented in a monograph, and the reader's knowledge is tested by the continuing medical education (CME) quiz. It will take the participant approximately 60 minutes to complete this lesson and quiz.

Evaluation: A course evaluation form will provide participants with the opportunity to review the content of the monograph, to identify future educational needs, and to comment on any perceived commercial or promotional bias in the presentation.

Evaluation Instrument: The 10-question, multiple choice CME quiz is used as the evaluation instrument.

Intended or Target Audience: This monograph is intended for obstetricians and gynecologists, family physicians, pediatricians, adolescent medicine specialists, nurse practitioners, nurse midwives, and others involved in reproductive health care.

CME Information: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dannemiller Memorial Educational Foundation and Emron. The Dannemiller Memorial Educational Foundation is accredited by the ACCME to provide continuing medical education for physicians.

The Dannemiller Memorial Educational Foundation designates this educational activity for up to 1 hour in Category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Provider approved by the California Board of Registered Nursing, Provider Number 4229 for 1 contact hour.

This continuing medical educational activity is made possible through an unrestricted educational grant from Wyeth-Ayerst Laboratories.